

# The Biomedical Aspects of Autism

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Over the last several decades, autism has become an increasingly prevalent developmental disorder that has received attention both in the medical and public communities. In the 1960's, the incidence was 1/10,000 which has since increased to 1/150 from 1991 to 1997. In 2007, more children were diagnosed with autism compared with diseases like cancer, diabetes, and AIDS combined. On average a new case of Autism is diagnosed every 20 minutes in the USA.<sup>1</sup> Autism costs more than \$90 billion a year nationwide, however, the research grant available for autism accounts only to 0.3% of the total NIH funding, which is still lower than what is available for other less common disorders.

Autism is more of a clinical syndrome than a disease. It is a behaviorally defined disorder.<sup>2</sup> It was first described by Leo Kanner in 1943,<sup>3</sup> and a milder form was described by a German doctor Hans Aspergers, now known as Asperger Syndrome.<sup>4</sup> Since then, many subtypes have been proposed and its cause, diagnosis and treatments remain controversial. This clinical syndrome is characterized by impaired social interaction, qualitative impairment in communication and restrictive, repetitive and stereotypic behaviors.

What is making Autism a fastest growing disorder and what's the etiology behind? Unfortunately, the identified etiology can only explain less than 15% of autism cases so far. Autism is truly a century mystery. Where is the missing piece of puzzle?

There has been a paradigm shift over the years. The old model considers Autism as incurable, genetically brain based disorder and is "prenatally hardwired". The new model, on the other hand, advocates that Autism is a genetically influenced but environmentally modulated systemic disorder, involving postnatal change in the brain and chemical imbalance with biological basis. It is "soft wired", therefore treatable or even curable.<sup>5-6</sup>

This article attempts to have a brief review of the different models to explain the etiology of autism.

**Neuropathology:** Autopsy data indicates enlarged brain size in autistic children. The brain weight is higher by 100-200g in 5-13 years old when compared with corresponding age and sex, predominantly inflammatory changes. Most head circumferences are also above average and approximately 20% of autistic children fall over 97<sup>th</sup> percentile. For the 18-

predominantly atrophic changes. Gross and microscopic pathology also showed overgrowth and enlargement of the white matter, cerebellum and related inferior olive atrophy. It also showed significant decrease in Purkinje cells regardless of age, sex and IQ level, and forebrain limbic system atrophy with abnormally small Hippocampus and shrieked Amygdala. There is strong evidence of inflammation and oxidative stress<sup>6</sup> in autistic brain tissue from childhood to middle age. There are also neurological activation responses, particularly in cerebellum. Responses are primarily from innate immunity. Cytokines are significantly elevated in brain and CSF of autistic patients. Furthermore, there is appreciable micro-vasculitis seen under microscope in their brain tissues.<sup>7-8</sup>

**Genetic etiology:** Autism has strong genetic component. Research indicated that there are more than 100 genes in different chromosomes related to Autism, for example, HOXA1, HOXA2 and HOXD1 on chromosome 7 are linked to cerebellum development; RELN and EN2 on chromosome 7 are related to language and speech development; serotonin transporter gene on chromosome 17 is contributing to OCD and depression symptom; GABA pathway gene is decreased in most autism patients; Autism subtype Rett Syndrome and Fragile X syndrome are X chromosome genetic disorder.<sup>9</sup>

Some polymorphism research indicates that most autistic patients are with IL-1 gene mutation also TH1 and TH2 immune imbalance. In addition many autistic patients are with significantly reduced liver detoxification mechanism, especially the glutathione conjugation. Furthermore, most autistic individuals have no glutathione-S-transferase gene on either chromosome (NULL). Other mutations have been seen in MTHFR1298C and C677T, cystathione beta synthase, catechol-O-methyltransferase, methionine synthase, superoxide dismutase, vitamin D receptor and nitric oxide synthase.<sup>10</sup> Recent finding of microdeletion/duplication on chromosome 16p11.2 in autism is one of the latest breakthroughs in which the role of chromosome imbalance in a heritable developmental disorder is observed and discussed.<sup>11</sup>

**Hypothesis:** Autism is genetically influenced but environmentally modulated systemic disorder. Genetically, autistic patients have reduced capacity of detoxification mechanism and impaired immune response. Environmentally, toxic load gradually increased over the years because of industry toxin, air pollution, increased vaccination and infectious agents. Furthermore, food structure change resulted in magnesium deficiency, reduced unsaturated fatty acid and vitamins. Over time, the interactions of genetic defect and toxic overload lead to systemic inflammation as a result of toxin accumulation and

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54 years old group, the brain weight decreases by 100-200g,

immune dysfunction. The major target organs are brain and gastrointestinal tract.

There are several theories for environmental factors as following.

**Heavy metal toxicity particularly mercury:** The mercury connection theory has drawn a hot debate over the last ten years. After thimerosal was removed from the vaccine in 2000, Autism incidence did not drop. This finding challenged but did not defeat the theory since there are other sources of mercury. In Texas, the correlation was found that for each 1000 pound of environmentally released mercury, there was 61% increase in the rate of autism. Clinically, there is strong evidence of correlation between mercury excretion by chelating and symptom improvement, and sometimes the improvement could be dramatic.<sup>12-13</sup>

**Chronic low grade infection:** Stool culture of autistic patients often showed positive report of bacteria or fungus. Clinically, there was significant improvement after antibiotics, anti-fungal or anti-viral agents for those implicated.<sup>11-13</sup>

**Gut and brain theory:** Most autistic patients have gastrointestinal symptoms such as increased flatulence, indigestion, malabsorption, chronic diarrhea, bloating etc. The intestinal permeability is mostly increased in autism. Clinically, gluten casein free diet alone offers significant improvement in 70% patients.<sup>14-15</sup>

**Immune dysfunction and autoimmune theory:** This theory has received increased attention over the last years after it identified several auto-antibodies and found elevated cytokines in brain among patients. Many autistic patients suffer from allergic problems. These are suggesting that autism is an immune disorder. The corresponding treatment developed for immune modulation, desensitization, anti-inflammatory agents are promising.<sup>16-17</sup>

**Oxidative stress<sup>6</sup> and mitochondria disorder:<sup>17</sup>** Some proposed autism is a free radical disease with the nature of multiple system involvement. Antioxidant and agents improve mitochondria energy metabolism proved their benefit in autism symptom relief.

With the biomedical researches of Autism, some new and experimental protocols have been established by the national autism institute, also known as Defeat Autism Now (DAN). This include such as special diets, nutritional supplements, detoxification, and heavy metal chelation, anti infection and antiinflammation, immune modulation. Some new treatments include Oxytocin,<sup>16</sup> HBOT,<sup>17</sup> Spirolactone, Lupron, etc.

There is currently no absolute cure for autism but new ideas are exciting and encouraging. Although the etiology of autism remains unclear, the future challenge is to identify with individual testing and target treatment appropriately.

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## Editorial Comment

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Autism is a complex disorder that is highly genetic yet variably modulated by internal and external environmental factors. Dr. Kong's comprehensive review on this topic captured the many aspect of our new understanding of autism. Autism is rather a multi-system biomedical problem than a pure behavioral neuropsychiatry problem. Such a paradigm shift not only provide new strategies for autism etiology studies where multiple factors, gene-gene interaction, gene-environment interactions should be considered simultaneously, more importantly, the problem associated with autism is more treatable than we used to think. The change of mindset regarding autism, as Dr. Kong said, offered hope for desperate parents and suffering patients.